REMARKS/ARGUMENTS

Claims 4-62 are pending.

Claims 1-3 have been cancelled.

Claims 10-14 and 17-18 have been withdrawn.

Claim 62 has been amended.

Support for the amendments is found in the claims and specification (e.g., page 5, the formula (I); the sequences of SEQ ID NO: 1-14, and claim 1), as originally filed.

No new matter is believed to have been added.

Applicants wish to thank the Examiner for indicating the allowable subject matter of claims 4-5, 8-9, and 36-39.

Claims 2, 6-7, 15-16, 19-35, and 40-62 are rejected under 35 U.S.C. 112, first paragraph, for lack of written description. Applicants respectfully traverse.

The purpose of the written description requirement is to ensure that a patent application conveys to a person of skill in the art that the applicants had possession of the claimed invention. *See, e.g., LizardTech, Inc. v. Earth Resource Mapping, Inc.,* 424 F3d 1336, 1345, 76 USPQ2d 1724, 1731 (Fed. Cir. 2005).

The present invention concerns peptides possessing improved affinity for phospholipids, toxicity, thermodynamic stability and reversibility of their folding processes when compared to prior art peptides such as the peptides disclosed in the article of Montaville et al, 2002, JBC, vol. 277, pages 24684-93 (previously submitted). *See* the present specification pages 1-4.

The claimed peptide sequence folds up in space so as to adopt its tertiary conformation, which is the active form of the peptide. Amino acids 12, 15, 16, 17, 19, 20, 22,

50, 55, 57, 58, 59, 60 and 65 are directly or indirectly involved in the binding to lipids, i.e. they are involved either in the three-dimensional structure of the peptide so that it adopts its active conformation allowing recognition of a negatively charged lipid, or in the peptide recognition site. *See* the present specification pages 3-8.

The amino acids J are the surface amino acids of this peptide when it is in its folded and active conformation. These residues are arranged spatially such that they are partially or completely exposed to the solvent.

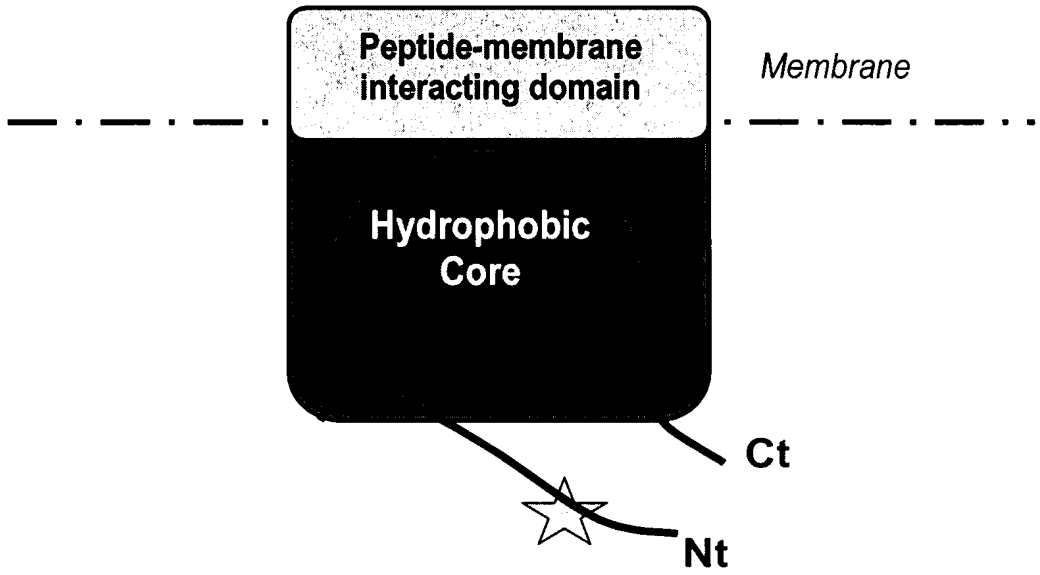
The Examiner has alleged that the specification does not specifically recite that **J^{26}** is only Leu, Val, Ile. However, Applicants have compare the sequences of SEQ ID NO: 1-14, as shown in Table A submitted with the response, and determined that in the sequence J^{26} is L, V, or I. The same is relevant to other positions, see Table A submitted with this paper showing residues of SEQ ID NO: 1-14 in each position.

Further, the Examiner is of the opinion that the specification does not provide a literal support for **claim 1** and "new" **claim 30**. However, claim 1 has been previously cancelled and claim 30 has been previously presented and is not "new". Claim 30 is based on original claim 30 directed to a kit and is further supported by the description on page 18 of the present specification.

Moreover, the Examiner has alleged that the specification does not provide examples wherein **J^{74}** is Cys, Lys, Pro or Orn. However, in claim 62 based on SEQ ID NO: 1-14, J^{74} is selected from Pro, Thr and Arg.

Concerning the similar topology of the annexin peptides falling within the sequence of claim 62, Applicants already explained in the previous response that the peptides of the present invention present improved properties in terms of affinity for phospholipids, toxicity, thermodynamic stability and reversibility of their folding processes when compared to prior art peptides.

The peptide subject-matter of the present invention presents the following diagrammatic structure which means that the peptides of the present invention share higher order secondary or tertiary structure :



As explained at paragraphs [0028] and [0034] of US2006/0148689 (published above-identified application 10/518,383), the domain directly or indirectly interacting with the membrane lipids mainly comprises the residues 12, 15, 16, 17, 19, 20, 22, 50, 55, 57, 58, 59, 60 and 65. These residues affect the peptide affinity for lipids and are clearly identified in the peptide sequence of Claim 62.

The stability and more generally the thermodynamic properties of the peptide subject-matter of the present invention mainly depend on the domain called "hydrophobic core" the residues of which are the residues U listed in Table 1 of claim 62. To improve the properties in comparison with annexin, it is necessary to choose a suitable combination of hydrophobic residues, but the solution is not, however, unique and Table 1 of claim 62 includes combinations deemed best.

The lower part of the peptide according to the invention includes, in particular, N-terminal and C-terminal segments to be used for various labels (for example, positioned at the star of the diagram) and/or grafting on various supports.

For surface residues of the peptide according to the invention, other than those mentioned above, there is a certain freedom of choice. It should be noted however that some of these amino acids were set in the peptide sequence of Claim 62 and on the basis of amino acids routinely found in the same position in SEQ ID NO. 1 to 14 of the appended sequence listing.

In addition, considering the Venn Diagram on the amino acid properties (see hereinafter), the list of amino acids for most of the variable J are amino acids which share physico-chemical properties.

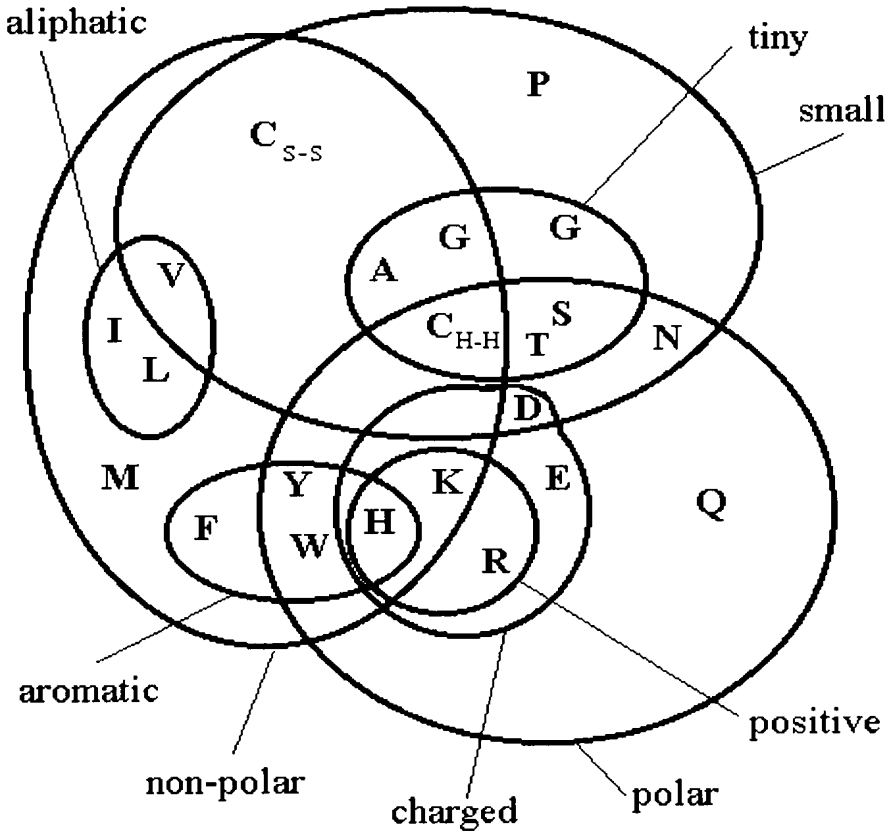


Figure 1. A Venn diagram showing the relationship of the 20 naturally occurring amino acids to a selection of physico-chemical properties thought to be important in the determination of protein structure (http://prowl.rockefeller.edu/aainfo/pchem.htm).

Applicants have compare the sequences of SEQ ID NO: 1-14 and divided the amino acids of the sequences in 3 different groups:

Group 1 : the amino acids that always represent a polar amino acid selected from the group consisting in Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Lys, Orn, Pro, Ser, Thr and Tyr (these amino acids are J^{1}, J^{3}, J^{13}, J^{21}, J^{27}, J^{31}, J^{33}, J^{34}, J^{36}, J^{45}, J^{49}, J^{51}, J^{61}, J^{63}, J^{66}, J^{74} and J^{75});

Group 2 : the amino acids that do not represent such a polar amino acid (these amino acids are J^{26}, J^{64}; J^{69} and J^{71}); and

Group 3 : the amino acids that can represent such a polar amino acid but can also represent another amino acid (these amino acids are J^{2}, J^{4}, J^{5}, J^{6}, J^{9}, J^{10}, J^{23}, J^{24}, J^{28}, J^{30}, J^{35}, J^{39}, J^{41}, J^{42}, J^{43}, J^{46}, J^{47}, J^{48}, J^{53}, J^{54}, J^{67}, J^{70}, and J^{73}).

The features concerning group 1 and group 2 have been previously introduced in the claims. In addition, as the amino acids J^{14}, J^{38}, J^{62} and J^{75} always represent an identical amino acid at each position 14, 38, 62, and 74 in sequences SEQ ID NO: 1-14, this feature is also present in the amended claims.

One skilled in the art knows from Group 1 the precise localization of these polar amino acids J and also knows that the last 5 polar amino acids cannot be selected in Group 2 but must be selected among the other amino acids which constitute Group 3.

The amino acids U are the core residues of the claimed peptide. In the folded and active conformation of the peptide, they are spatially arranged close to one another and are not exposed to the solvent. They constitute the hydrophobic core of the protein. The compact assembly of the atoms of these residues plays a predominant role in the stability of the peptide in its active conformation. The amino acids U at each identified position are selected from a limited number of residues (at most 5). *See* the present specification pages 6-7.

Further, in Claim 62 the peptides comprise the sequence (I') with amino acids U as defined in Table 1 and the specific amino acids at positions 7, 12, 14, 16, 17, 19, 20, 22, 32, 37, 38, 50, 55, 57, 58, 60, 62 and 75 as defined in the sequences of SEQ ID No: 1-14 of the sequence listing.

The function of the residue X^{18} is to maintain the structure of the Gly-X-Gly loop in the active form of the peptide, in particular where the residues Z^{59} and Z^{65} are Glu, to modulate the hydrophobic and lipophilic nature of this loop, and to provide new specific interactions with phospholipids. This is the case, for example, of the residues Asn, Cys, Ser, Thr, Trp and Tyr. *See* the present specification page 7.

The residues Z^{59} and Z^{65} are advantageously lysine residues, the effect of which is to replace the calcium ion with the positively charged $-NH_3^+$ group of the lysine and to improve

the affinity of the peptide for a negatively charged membrane. *See* the present specification pages 7-8.

The peptide of the sequence (I'), in its active form, comprises three sites for binding to a calcium ion where the calcium ion complexed with this site constitutes one of the ligands of a negatively charged phospholipid. The first of these sites, called principle site, involves residues 15, 18, 19 and 59 as calcium ligands. The second of these sites, called secondary site, involves residues 20 and 22 as calcium ligands. The third of these sites, which is a low-affinity secondary site, involves residues 57, 60 and 65 as calcium ligands. Thus, the residues involved overall in the binding to phospholipids are residues 12, 15, 16, 19, 20, 22, 50, 55, 57, 58, 69, 60 and 65. This list includes residues involved in calcium binding, the phospholipids being calcium ligands. *See* the present specification pages 8-11.

Because of the improved properties and the labeling, the claimed peptides are useful for detecting not only *in vitro* but also *in vivo,* e.g., apoptotic cells or foci and negatively charged lipids at the surface of the cells. *See* the present specification, pages 1-3, the Examples.

Thus, the scope of the peptide sequence of Claim 62 has been restricted so that the amino acids are clearly identified.

In Claim 62, each amino acid J^x is defined by a Markush list corresponding to the different amino acids at position x in the sequences SEQ ID NO: 1-14.

Thus, it is possible to define more precisely the other residues and mainly surface residues. In particular, among these residues, the localization of the polar amino acids that are selected from the group consisting of Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Lys, Orn, Pro, Ser, Thr and Tyr has been defined more precisely.

The peptide sequence (I') of Claim 62 has clearly identified amino acids. Also, the amino acids are identified at the positions involved in the affinity for phospholipids, toxicity, thermodynamic stability and reversibility of their folding processes.

It is therefore clear that the peptides comprising the peptide sequence as defined in Claim 62 can solve the technical problem of the present invention.

Thus, it is believed that the specification provides an adequate description for the genus of the clamed peptide.

Applicants request that the rejection be withdrawn.

In response to the rejection under 35 U.S.C. 112, second paragraph, Applicants reintroduced unintentionally deleted variable J36 and request that the rejection be withdrawn.

A Notice of Allowance for all pending claims is requested.

Respectfully submitted,

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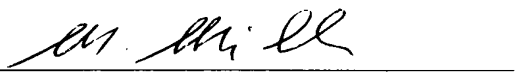

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Table A

		1	2	3	4	5	6	7	8	9	10	11	12	13	14
															G
															S
															G
															C
														G	G
														S	T
														E	E
												G		C	T
												S	G	D	D
												G	S	F	F
												C	P	P	P
J1		G	N	D	G	G	G	P	H	G	G	G	G	G	G
J2		F	F	F	F	F	F	G	F	F	F	F	F	F	F
J3		D	D	S	N	D	N	D	N	D	D	D	D	D	D
J4		E	A	P	A	P	P	A	P	P	V	E	E	E	E
J5		R	E	S	M	N	D	I	D	L	D	R	R	R	R
J6		A	R	V	E	Q	A	R	P	R	R	A	A	A	A
Z7		D	D	D	D	D	D	D	D	D	D	D	D	D	D
U8		V	A	A	A	A	A	A	V	A	A	V	V	V	V
J9		E	L	E	Q	E	K	E	E	E	K	E	E	E	E
J10		T	N	A	T	A	A	I	T	V	K	T	T	T	T
U11		L	I	I	K	L	L	L	L	L	L	L	L	L	L
J12		R	R	R	R	R	R	R	R	R	R	R	R	R	R
J13		K	K	K	K	T	K	K	K	K	K	K	K	K	K
J14		A	A	A	A	A	A	A	A	A	A	A	A	A	A
U15		M	I	I	M	M	M	M	M	M	M	M	M	M	M
J16		K	K	K	K	K	K	K	K	K	K	K	K	K	K
J17		G	G	G	G	G	G	G	G	G	G	G	G	G	G
J18		L	M	I	L	F	L	F	I	F	M	TML	L	LMT	LMT
J19		G	G	G	G	G	G	G	G	G	G	G	G	G	G
J20		T	V	T	T	S	T	T	T	T	T	T	T	T	T
J21		D	D	D	D	D	D	D	N	D	N	D	D	D	D
J22		E	E	E	E	E	E	E	E	E	E	E	E	E	E
J23		E	D	D	D	E	D	Q	Q	Q	A	E	E	E	E
J24		S	T	M	A	A	T	A	A	A	A	S	S	S	S
U25		I	I	L	I	I	I	I	I	I	I	I	I	I	I
J26		L	V	I	I	L	I	V	I	I	I	L	L	L	L
J27		T	N	S	S	D	D	D	D	D	E	T	T	T	T
J28		L	I	I	V	I	I	V	V	C	I	L	L	L	L
U29		L	L	L	L	I	I	V	L	L	L	L	L	L	L
J30		T	T	T	A	T	T	A	T	G	S	KT	T	TK	YK
J31		S	N	E	Y	S	H	N	K	S	G	S	S	S	S
J32		R	R	R	R	R	R	R	R	R	R	R	R	R	R
J33		S	S	S	N	S	S	S	S	S	T	S	S	S	S
J34		N	N	N	T	N	N	N	N	N	S	N	N	N	N
J35		A	A	A	A	R	V	D	T	K	D	A	A	A	A
J36		Q	Q	Q	Q	Q	Q	Q	Q	Q	E	Q	Q	Q	Q

B37		R	R	R	R	R	R	R	R	R	R	R	R	R	R
J38		Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q
J39		E	D	L	E	E	Q	K	T	Q	Q	E	E	E	E
U40		I	I	I	I	V	I	I	I	I	I	I	I	I	I
J41		S	A	V	R	C	R	K	A	L	K	KS	S	SK	SK
J42		A	F	K	T	Q	Q	A	K	L	Q	A	A	A	A
J43		A	A	E	A	S	T	A	S	S	K	A	A	A	A
U44		Y	Y	Y	Y	Y	F	F	F	F	Y	YF	Y	FY	FY
J45		K	Q	Q	K	K	K	K	K	K	K	K	K	K	K
J46		T	R	A	S	S	S	T	A	T	A	ET	T	TE	TE
J47		L	R	A	T	L	H	S	Q	A	T	L	L	L	L
J48		F	T	Y	I	Y	F	Y	F	Y	Y	F	F	F	F
J49		G	K	G	G	G	G	G	G	G	G	G	G	G	G
J50		R	R	R	R	R	R	R	R	R	R	R	R	R	R
J51		D	E	E	D	D	D	D	D	D	E	D	D	D	D
U52		L	L	L	L	L	L	L	L	L	L	L	L	L	L
J53		L	A	K	I	I	H	I	T	I	E	L	L	L	L
J54		D	S	D	D	A	T	K	E	K	E	D	D	D	D
J55		D	D	D	D	D	D	D	D	D	D	D	D	D	D
U56		L	L	L	L	L	L	L	L	L	L	L	L	L	L
J57		K	K	K	K	K	K	K	K	K	K	K	K	K	K
J58		S	S	S	S	S	S	S	S	S	S	S	S	S	S
Z59		E	E	E	E	E	E	E	E	E	E	KG	E	EK	EK
J60		L	L	L	L	L	I	L	L	L	L	L	L	L	L
J61		T	S	S	S	T	S	S	S	S	S	T	T	T	T
J62		G	G	G	G	G	G	G	G	G	G	G	G	G	G
J63		K	H	H	N	K	D	N	K	N	N	K	K	K	K
J64		F	L	F	F	F	L	M	L	F	F	F	F	F	F
Z65		E	E	E	E	E	E	E	E	E	E	KE	E	EK	EK
J66		K	R	R	R	R	R	R	R	K	K	K	K	K	K
J67		L	V	L	V	L	L	L	L	T	T	LE	L	EL	EL
U68		V	I	M	I	I	I	I	I	I	A	V	V	V	V
J69		V	L	V	V	V	L	L	V	L	L	V	V	V	V
J70		A	G	A	G	G	G	A	A	A	A	A	A	A	A
J71		L	L	L	M	L	L	L	L	L	L	L	L	L	L
U72		L	L	V	M	M	M	F	M	M	L	L	L	L	L
J73		K	K	T	T	R	M	M	Y	K	D	K	K	K	K
J74		P	T	P	P	P	P	P	P	T	R	P	P	P	P
J75		S	S	S	S	S	S	S	S	S	S	S	S	S	S
														R	R